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LESS IS MORE IN INTENSIVE CARE

Less is more: critically ill status is not a carte blanche for unlimited antibiotic use

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The film "Blade Runner 2049" depicts a bleak view of humanity 30 years from now, a world in which survival will be much more difficult than today. You may say we are lucky that it is only 2020; however, we are already facing a growing and unstoppable shortage of antibiotics worldwide due to bacterial resistance, and this could end up in a humanitarian disaster. The CDC recently reported that the pace of antibiotic-resistant infections and its associated mortality are on the rise [1].

Can you imagine a world without antibiotics? No antibiotics would preclude the performance of most surgeries, cancer treatments, solid organ and hematopoietic transplantation, and no treatment for pneumonia, abdominal infections, urinary tract infections, skin/soft tissue infections, diarrhea, meningitis, and obviously no treatment for sepsis! The lack of antibiotics would undoubtedly lead to millions of deaths globally. While it is inevitable that any antibiotic eventually weakens its efficacy because of the natural selection pressure, we have concrete ways in our hands to slow this fate. In this article, we propose bedside practical solutions to mitigate this rapid progression of antibiotic loss.

The single most important risk factor for the development of antibiotic resistance is the overuse of antibiotics in both humans and animals [2]. The use of antimicrobials for veterinary care, and oral antibiotics for medical care are out of this article's scope, but note that the antibiotic overuse in these two settings is also involved in the development of bacterial resistance. Health-care providers utilize antibiotics in a daily basis—knowing that the overuse, which represents inappropriately excessive administration of antibiotics, is the accelerating drive of bacterial resistance—then, a begging question must be answered: Who is responsible for most intravenous antibiotic use? Given that more than half of ICU patients receive antimicrobial therapy [3], it should not take a rocket scientist to estimate the answer. Which patients end up receiving the majority of empiric intravenous antibiotics? The answer is obvious—critically ill patients. And where critically ill patients are most commonly located? In the emergency department before hospital admission and in the intensive care unit (ICU) after the hospital admission. What health-care providers who take care of critically ill patients (emergency department physicians, intensivists, anesthesiologists, pulmonologists, infectologists, clinicians and surgeons) can do to curb the fate of antibiotic loss?

Compliance with individual hand hygiene, hospital infection control measures and antibiotic stewardship programs are critical to win the fight against bacterial resistance, and this has been discussed elsewhere [4, 5]. In addition, we propose that health-care providers can bring concrete and direct benefits to each of our critically ill patients at the bedside by preventing the excessive use of unnecessary antibiotics. How can this be done?

The clinical deterioration of mechanically ventilated patients may be associated with a new infection process; however, the majority of ventilator-associated events leading to antibiotic administration is related to non-infectious processes [6]; thus, the appropriate antimicrobial de-escalation is essential and can be safely done if culture results are negative [7, 8]. Of note, if the clinical deterioration progresses to septic shock, then microbiological samples should be taken and antibiotics be immediately started.

For many decades, critically ill patients have been treated with antibiotics during two to three weeks for severe infections including pneumonias, abdominal and

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urinary infections, all of which still comprise the majority of infections leading to sepsis and admission to the intensive care unit. This practice was based on zero scientific evidence! However, physicians are also creatures of habits, good and bad habits, and the habits of giving prolonged courses of antibiotics have been the standard of care around the world. More recently, several randomized controlled trials have brought relevant findings to our clinical practice, specifically regarding the efficacy of short-course antibiotics in the setting of several bacterial infections. Table 1 shows the proven treatments with short course of antibiotics.

Another important way to reduce both the development of resistance and the unnecessary prolongation of antibiotics is by administrating antibiotics according to the most optimal pharmacokinetics and pharmacodynamics (PK/PD) parameters. The appropriate antibiotic dosing will clear the infection faster than suboptimal dosing and consequently will speed up the clinical cure rate, which will give the clinician the indication that is safe to de-escalate antibiotics [8]. In fact, the hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) guideline from the Infectious Disease Society of America and the American Thoracic Society [7] recommends the use of PK/PD for antibiotic dosing in patients with HAP or VAP. Considering that respiratory infections are the most common cause of sepsis worldwide, it is no surprise that pneumonia is among the main drives of antibiotic use in the ICU. The vast majority of hospital-acquired and ventilator-associated pneumonias can be safely treated with an average of 7 days of antibiotics independent of the microbial etiology [7]. The benefits from the PK/PD approach have also been demonstrated in patients with sepsis and septic shock [9, 10]. There are three other respiratory syndromes that are responsible for a substantial overuse of antibiotics in the ICU: COPD exacerbation, ventilator-associated tracheobronchitis (VAT) and health-care associated pneumonia (HCAP). COPD exacerbation is not and should not be treated as pneumonia, and evidence clearly supports a very short course of just a few days of antibiotics, if any, because one-third or more of these exacerbations are caused by viruses [11]. VAT is an ill-defined syndrome with low-quality scientific evidence, poorly predictive of progression to VAP and not associated with higher mortality than ICU patients without VAT; this led the IDSA/ATS guideline to recommend against the use of antibiotics in patients with suspected VAT [7]. HCAP has now been eliminated from both the HAP/VAP and the CAP guidelines [7, 12] because the most current evidence does not support the historical assumption that the HCAP definition could distinguish patients with versus without MDR pneumonia. Hence, the avoidance of empiric antibiotics in patients with suspected HCAP or VAT without VAP can further prevent a substantial amount of unnecessary antibiotic overuse in the ICU. In addition, antibiotics should be avoided in patients with positive urine culture with normal urine analysis, except in certain immunocompromised patients, such as renal transplant recipients.

Another area of interest is regarding the use of combination versus monotherapy for critically ill patients. While we agree that the use of combination antibiotic

Table 1 Practical bedside recommendations to minimize unnecessary antibiotic exposure in the critically ill patient

Prerequisites:
Standard patient protection by the infection control program
Compliance with hand hygiene
Control of transmission of multi-drug-resistant bacteria
1. Collect microbiological samples before starting antimicrobial therapy, given individual patient's clinical presentation
2. Use proven effective short-course antibiotic regimens:
(a) Hospital-acquired and ventilator-associated pneumonia: 7 days
(b) Community-acquired pneumonia: 5 days
(c) Acute exacerbation of chronic bronchitis: 3 days
(d) Complicated intra-abdominal infections: 4 days
(e) Complicated urinary tract infection: 5 days
3. Do not start broad-spectrum antibiotics for the outdated HCAP definition. Instead, use the MDR risk factors from the HAP/VAP and CAP guidelines
4. Do not administer antibiotics for VAT without indication of pneumonia
5. Do not use combination antibiotic therapy for known susceptible bacterial infections
6. Address source control as rapidly as possible (e.g., catheter removal, abscess drainage)
7. Optimize antibiotic pharmacokinetics and pharmacodynamics (PK/PD) parameters
8. De-escalate antibiotics when patient is showing clinical improvement and/or cultures are negative

for the empiric treatment of severe infections in critically ill patients may be a reasonable strategy while microbiology tests are being processed, we do not recommend combination therapy when the infectious pathogen and susceptibilities are known, i.e., targeted/directed therapy. Evidence suggests that combination antibiotic therapy does not prevent development of resistance, is associated with more side effects and does not improve survival compared to monotherapy [13–16]. For the high mortality risk cases of bloodstream infection due to carbapenemase-producing Enterobacteriaceae, the potential value of combination over monotherapy remains to be determined.

Lastly, we cannot emphasize enough the critical importance of an aggressive source control of the infection process in the critically ill patient. More antibiotics and prolonged courses will not suffice if there is an uncontrolled source of infection (e.g., abdominal abscess, infected central venous catheter, empyema). In fact, the antibiotic escalation may do more harm than good in this situation. On the other hand, antibiotic de-escalation can produce further benefits when patients are presenting clinical improvement. Importantly, the lack of de-escalation (i.e., unnecessary prolonged courses) can harm patients and lead to more antibiotic resistance [7, 17–19].

It is time to take action and protect our critically ill patients from the harmful effects of unnecessary antibiotic overexposure. This will not only benefit our current patients at the bedside by preventing serious antimicrobial side effects and *C difficile* colitis, but will also save future patients from dying due to multi-drug-resistant infections. Our 2020 bedside actions to prevent antibiotic overuse can curtail the development of antibiotic resistance and beat the Blade Runner's gloomy prediction for 2049.

Electronic supplementary material
The online version of this article (https://doi.org/10.1007/s00134-020-06260-7) contains supplementary material, which is available to authorized users.

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Compliance with ethical standards

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